Engineered extracellular vesicles with high collagen-binding affinity present superior in situ retention and therapeutic efficacy in tissue repair.

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Public Summary:
Stem cell derived extracellular vesicles (EVs) have been thoroughly researched for their therapeutic potential to treat many diseases. Extracellular vesicles encapsulate particles secreted by cells that regulate cellular functions and help cellular communication. When secreted from stem cells, they have been observed to secrete proteins that protect neurons and promote cellular regeneration. However, the therapeutic potential and translational application of EVs are limited due to rapid diffusion after administration. In this study, we developed collagen binding, stem cell derived EVs to improve EV retention, cellular regeneration capabilities, and therapeutic efficacy after transplantation. Mesenchymal stem/stromal cell surfaces were conjugated with molecules, SILY (SILY-EVs), that possess high collagen affinity to anchor them to the collagen backbone of the extracellular matrix found in connective tissue all over the body. The SILY-EVs significantly increased EV adhesion to the collagen backbone of the ECM in an in vitro analysis and did not alter the EVs' biological functions. The therapeutic efficacy of this treatment was also evaluated in a mouse hind limb ischemia model and results demonstrated SILY-EVs presented longer retention, suppressed inflammatory responses, and significantly augmented muscle regeneration and vascularization, compared to the unmodified EVs. With a high distribution of collagen in tissues and organs, SILY-EVs have great therapeutic potential to treat various diseases. Moreover, results of this study demonstrate SILY-EVs can functionalize collagen-based biomaterials and deliver therapeutic agents for regenerative medicine applications.

Scientific Abstract:
Although stem cell-derived extracellular vesicles (EVs) have remarkable therapeutic potential for various diseases, the therapeutic efficacy of EVs is limited due to their degradation and rapid diffusion after administration, hindering their translational applications. Here, we developed a new generation of collagen-binding EVs, by chemically conjugating a collagen-binding peptide SILY to EVs (SILY-EVs), which were designed to bind to collagen in the extracellular matrix (ECM) and form an EV-ECM complex to improve EVs' in situ retention and therapeutic efficacy after transplantation. Methods: SILY was conjugated to the surface of mesenchymal stem/stromal cell (MSC)-derived EVs by using click chemistry to construct SILY-EVs. Nanoparticle tracking analysis (NTA), ExoView analysis, cryogenic electron microscopy (cryo-EM) and western-blot analysis were used to characterize the SILY-EVs. Fluorescence imaging (FLI), MTS assay, ELISA and reverse transcription-quantitative polymerase chain reaction (RT-qPCR) were used to evaluate the collagen binding and biological functions of SILY-EVs in vitro. In a mouse hind limb ischemia model, the in vivo imaging system (IVIS), laser doppler perfusion imaging (LDPI), micro-CT, FLI and RT-qPCR were used to determine the SILY-EV retention, inflammatory response, blood perfusion, gene expression, and tissue regeneration. Results: In vitro, the SILY conjugation significantly enhanced EV adhesion to the collagen surface and did not alter the EVs' biological functions. In the mouse hind limb ischemia model, SILY-EVs presented longer in situ retention, suppressed inflammatory responses, and significantly augmented muscle regeneration and vascularization, compared to the unmodified EVs. Conclusion: With the broad distribution of collagen in various tissues and organs, SILY-EVs hold promise to improve the therapeutic efficacy of EV-mediated treatment in a wide range of diseases and disorders. Moreover, SILY-EVs possess the potential to functionalize collagen-based biomaterials and deliver therapeutic agents for regenerative medicine applications.